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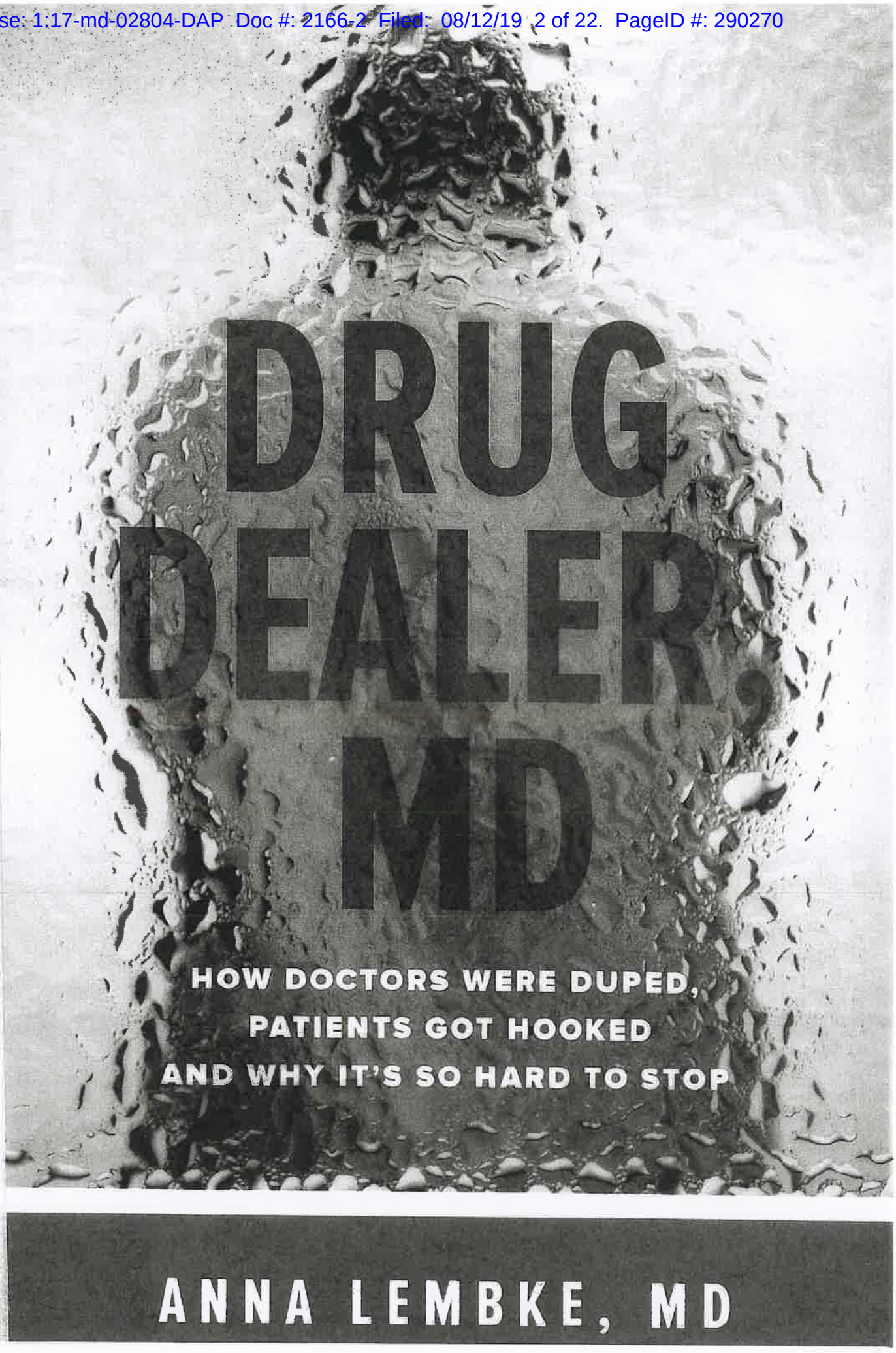
DRUG DEALER, MD
HOW DOCTORS WERE DUPED, PATIENTS GOT HOOKED AND WHY IT'S SO HARD TO STOP
ANNA LEMBKE, MD

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How Doctors Were Duped, Patients Got Hooked, and Why It's So Hard to Stop

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JOHNS HOPKINS UNIVERSITY PRESS | *Baltimore*

Printed in the United States of America on acid-free paper
9 8 7 6 5 4 3 2 1

Johns Hopkins University Press
2715 North Charles Street
Baltimore, Maryland 21218-4363
www.press.jhu.edu

Library of Congress Cataloging-in-Publication Data

Names: Lembke, Anna, 1967–
Title: Drug dealer, MD : how doctors were duped, patients got hooked, and why it's so hard to stop / Anna Lembke, MD.
Description: Baltimore : Johns Hopkins University Press, 2016. | Includes bibliographical references and index.
Identifiers: LCCN 2016010031 | ISBN 9781421421407 (pbk. : alk. paper) | ISBN 1421421402 (pbk. : alk. paper) | ISBN 9781421421414 (electronic) | ISBN 1421421410 (electronic)
Subjects: LCSH: Analgesics. | Medication abuse. | Physician and patient. | Drugs—Prescribing. | Drug addiction.
Classification: LCC RM319 .L46 2016 | DDC 615.7/83—dc23
LC record available at http://lccn.loc.gov/2016010031

A catalog record for this book is available from the British Library.

Special discounts are available for bulk purchases of this book. For more information, please contact Special Sales at 410-516-6936 or specialsales@press.jhu.edu.

Johns Hopkins University Press uses environmentally friendly book materials, including recycled text paper that is composed of at least 30 percent post-consumer waste, whenever possible.

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Big Pharma Joins Big Medicine

Co-opting Medical Science to Promote Pill-Taking

Jim lay flat on his back in a hospital bed, morphine seeping into his veins through a long, thin, transparent tube. He felt no pain of any kind, and yet he continued to be obsessively preoccupied with his next dose of pain medication. As the time approached, he counted the minutes and seconds until he could ring the nurse and ask for more. She wouldn't just give it for free, however; he had to answer her questions the right way. She would always ask the same question before she could administer the meds: "On a scale from 1 to 10, how bad is your pain, with 0 being no pain, and 10 being the worst pain you could possibly imagine."

After years of manipulating people to manage, or attempt to manage, his drinking, Jim had developed a deep understanding of certain aspects of human psychology, especially how to appear trustworthy while lying. In this instance, he applied those skills, because he was not in fact having much if any pain by day three into his hospitalization. But he wanted those opioids.

He figured that if he said "10," he would be seen as someone who exaggerated. If he said anything less than "7," he might not get his mor-

phine, which he already thought of as his. So he said, "My pain is real bad, it's a 7," going for the middle of the road approach as a way to appear reasonable but still sufficiently distressed. Whether due to Jim's skillful psychological manipulation or not, "7" worked every time, and Jim managed to get intravenous morphine every four hours continuously for his entire hospital stay, which lasted about a week.

There was only one moment when Jim suspected that he was in trouble. It was a conversation with one of his nurses.

"Jim," said the nurse, "You're taking a lot of this stuff, and I'm worried. I've seen so many people come through here and end up sicker than when they started because of these pain meds. They get hooked. I don't want that to happen to you. So if you could cut back, that would be good. But if you tell me you're in pain," she added, as if catching herself, "I'll give it to you every time."

Very quiet and distant alarm bells rang in Jim's brain, but they were too quiet and too distant to compete with his overwhelming craving for the next dose of morphine.

"I can handle it," he told her, "and I'm in pain."

This interaction between Jim and his nurse is crucial to understanding the rapid rise in prescription opioid addiction and opioid-related deaths. Jim's nurse knew on some level that Jim was getting too many opioids, and she even admitted to seeing patients "end up sicker than when they started" because of the amount of opioids they received while hospitalized. But despite her misgivings, she felt pressure to follow the standardized protocol: no cumulative dose or duration of opioids is too high for a patient still endorsing pain.

Curing Doctors of Their "Opioiphobia"

The prolific opioid prescribing that characterized the 1990s and 2000s and that continues today, at a galloping although somewhat slower pace, represents a radical shift in practice. Prior to 1980, doctors used opioid pain relievers sparingly, and only for the short term in cases of

severe injury or illness, or during surgery.[77, 78] Their reluctance to use opioids for an extended length of time, despite their short-term effectiveness for pain, sprang from fear of causing addiction.*

In the early 1980s, however, professional medical opinion on the use of opioid pain relievers began to change, in favor of using opioids more liberally. The number of patients living with pain was growing, due to an aging population, to more people undergoing and surviving complicated surgeries, and to more people being kept alive with life-threatening illnesses. A new movement, known as hospice care, was beginning to make inroads in the United States at this time as well, advocating for more aggressive comfort care at the end of life.

What began as a good faith effort to improve the lives of patients in pain soon gave way to an epidemic of opioid painkiller overprescribing. The pharmaceutical industry (Big Pharma), specifically the makers of opioid painkillers like OxyContin (Purdue Pharma), played a pivotal role in the epidemic. But to ascribe all the blame to Big Pharma is to oversimplify. The pharmaceutical industry was able to influence doctor-prescribing only by joining together with academic physicians, professional medical societies, regulatory agencies (the Federation of State Medical Boards and The Joint Commission), and the Food and Drug Administration. Together, these different factions manipulated and misrepresented, deliberately or otherwise, medical science to serve their own agendas.

The Role of Academic Physicians

It had been common practice before 2000 for doctors to accept gifts, meals, payments, travel, and other services from companies that made

*The United States endured two opioid epidemics in the twentieth century, the first in the early 1900s, when heroin was marketed alongside Bayer aspirin as a remedy for numerous minor ailments. The second, in the 1960s, coincided with the Vietnam War and again involved mostly heroin, although by then heroin was illegal. These prior experiences with opioids made the medical community understandably reluctant to repeat history's mistakes.

the drugs and medical products they might recommend to their patients.*[79] Many of these overt attempts to influence doctors have since been banned by hospitals and other health care institutions across the country, in recognition that even a free pen and half an hour of a drug representative's time can unduly influence prescribing practices. An analysis published by the *Journal of the American Medical Association* found that doctors who accept perks from drugmakers are more likely to prescribe that drugmaker's brand of drugs.[80] Recent federal legislation demands that doctors who receive financial reimbursement from a drug or medical supply company disclose those payments. In September 2014, the Sunshine Act required that all corporate payments to physicians worth $10 or more be published in an online database, in hopes that more transparency would alert patients to which doctors might be unduly influenced by industry.[79] These changes discouraged many doctors from openly taking gifts from Big Pharma.

Big Pharma responded by changing tactics. Instead of influencing doctor-prescribing by giving perks directly to doctors, it instead enlisted the help of academic researchers to promote its products, while itself remaining invisible, in the background. Big Pharma dubbed these doctors "thought leaders," choosing only researchers whose results favored their drug. They paid for thought leaders to travel across the country presenting their work at medical conferences and so-called informational seminars. Pharmaceutical companies were careful not to overtly associate their thought leader's message with their brand. They often paid thought leaders large sums of money to speak, and in some

*The pharmaceutical industry also engages in direct-to-consumer advertising, that is, it markets to patient consumers directly. Most people are familiar with Pharma ads on TV promoting better sleep, hotter sex (or for the middle-aged and older, any sex at all), less pain, and more joy. These commercials frequently depict an ecstatic woman running through a field of springtime flowers, butterflies alighting on her shoulders, and ending with the phrase "Ask your doctor if drug X is right for you." This kind of advertising can influence prescribing because doctors are eager to please their patients, and when a patient asks about a particular medication, a doctor may prescribe it over other comparable choices.

instances provided the funds to subsidize the entire medical conference/seminar. They promoted the drug company's product, while also furthering their elected thought leader's academic career.

This insidious yet incredibly powerful method—what amounts to a Trojan Horse of drug peddling—represents a betrayal of the average doctor seeing patients. The average clinician relies on his or her academic colleagues to present unbiased research. When the average doctor attends an academic conference, he or she trusts that the organizers of the conference will feature speakers who represent diverse and scientifically valid viewpoints.

New York Times journalist Barry Meier, in his excellent book *Pain Killer*,[81] describes how Big Pharma chose Dr. Russell Portenoy as their "thought leader," supporting his travel around the country to promote more liberal opioid prescribing for many types of pain. Dr. Portenoy's talks were sponsored by drug companies or by the Dannemiller Foundation, an organization paid by drug companies to put on continuing medical education programs for doctors. Dr. Portenoy had financial relationships with at least a dozen companies, most of which produced prescription opioids.[81]

The first misconception about opioid painkillers conveyed to doctors by Dr. Portenoy and others is that these drugs are effective for the treatment of chronic pain (pain lasting three or more months). The benefit of short-term opioid therapy is supported by multiple clinical trials,[82] but there is very little evidence to support the use of opioids for managing chronic pain, and the risks of long-term use may outweigh the benefits.[83] One of the risks, paradoxically, may be an increase in pain due to a phenomenon called "opioid induced hyperalgesia" (OIH), "hyper" for "more/over," and "algesia" for "pain." Animal and human studies show that prolonged use of opioid painkillers can cause heightened sensitivity to pain and result in pain syndromes that did not previously exist.[84] One small prospective study of six patients with chronic lower back pain started on oral morphine demonstrated that all six developed hyperalgesia (increased sensitivity to pain) after four weeks.[85]

The second misconception is that no dose of opioid painkillers is too high for the treatment of pain. In fact, we know that tolerance to the pain-relieving effects of opioids occurs in most individuals after weeks to months, at which point the opioids stop working, no matter how high the dose. The risk of side effects, however, rises in a dose-depending manner[83]—the higher the dose, the worse the side effects, including the risks of addiction and death due to accidental overdose.

Dr. Portenoy based his false assertions on a study he had published in 1986 with Dr. Kathleen Foley in a medical journal simply called *Pain*. The study was a review of thirty-eight patients with chronic pain treated with opioid painkillers. Portenoy and Foley wrote that "opioid maintenance therapy can be a safe, salutary and more humane alternative . . . in those patients with intractable non-malignant pain and no history of drug abuse."[86] This statement represents a plea for a departure from previous practice, in which opioids were used almost exclusively for acute (after surgery or injury) and palliative (at the end of life) pain. The authors also go on to say that no amount of opioids to treat chronic pain is too much, again flying in the face of convention, which had always advocated using the bare minimum to avoid the risks of death due to respiratory suppression and addiction: "We disagree with the concept of setting a maximum dose. The pharmacology of opioid use in the treatment of pain is based on dose titration to effect."[86]

Portenoy and Foley's review of thirty-eight patients does not, however, constitute a high level of scientific evidence. It did not include a large number of patients. There was no comparison group taking a placebo or getting some other treatment for pain, such as physical therapy. It was retrospective rather than prospective, meaning that the authors asked patients to recollect past experiences, biased by recall effects, rather than soliciting their reactions going forward in real time. Although these patients endorsed improvements in pain with opioids, they did not report any functional improvement. Yet this study became very well known in the medical community, and its publication and dis-

semination correlated with a sudden uptick in the rate of opioid prescriptions for patients with chronic pain.[87]

As Portenoy's talks drew ever larger crowds, he frequently referenced other publications that supported his view.[81] He invoked a 1980 *New England Journal of Medicine* letter to the editor entitled "Addiction Rare in Patients Treated with Narcotics." The letter reported that among hospitalized patients taking opioids for pain, clinical researchers had found "only four cases of addiction among 11,882 patients treated with opioids."[46] This letter was widely cited by doctors and medical organizations and frequently quoted by the pharmaceutical industry in its advertisements for opioids, as proving that "less-than-1%" of patients receiving opioids for pain become addicted.[81] This misconception—that as long as doctors were prescribing opioids for the treatment of pain, there was less than a 1 percent chance of their patients becoming addicted—was perhaps the most egregious. It implied that the well-known inherent addictive potential of opioids was magically eliminated by the halo of a doctor's prescription. We know now that opioid painkillers prescribed by a doctor are as addictive as heroin purchased on a street corner.

The final misconception perpetuated by the pseudoscience of this era was the idea of "pseudoaddiction." Based on a single case report of a patient who engaged in drug-seeking behavior due to inadequate pain control,[88] doctors were taught that any patient prescribed opioid painkillers who demonstrates drug-seeking behavior is not addicted, but in pain. The solution? Increase the dose of opioid painkillers. We know that many patients have severe debilitating pain, and sometimes the appropriate intervention is to increase the opioid painkillers. But some patients who report pain and are engaging in drug-seeking behavior are addicted to opioids. They may also have untreated pain. To help this population, doctors need to recognize and treat both disorders, not ignore the possibility of addiction.

In a taped interview with Dr. Russell Portenoy in 2011, on the web-

site for the advocacy group Physicians for Responsible Opioid Prescribing (PROP),[89] Portenoy describes his unabashed advocacy for opioids in the 1990s and early 2000s as follows: "I gave so many lectures to primary care audiences in which the Porter and Jick article[46] was just one piece of data that I would then cite. I would cite 6 to 7 maybe 10 different avenues of thought or evidence, none of which represents real evidence. And yet what I was trying to do was to create a narrative so that the primary care audience would look at this information in toto and feel more comfortable about opioids in a way they hadn't before. . . . Because the primary goal was to de-stigmatize, we often left evidence behind."[89]

The Role of Professional Medical Societies

Every medical specialty, from family medicine to orthopedic surgery, has medical societies created by and for the doctors who practice it. The purpose of a medical society is to promote the specialty and its doctors and also, theoretically, to advocate for patients.

Beginning in the 1980s, pain societies campaigned for better treatment of patients with pain, including arguing for more liberal use of opioid painkillers in the treatment of pain. On the face of it, their intentions were noble. But closer scrutiny reveals that some of these pain societies were financially subsidized by drug manufacturers and as such were biased. They helped propagate data that turned out to be untrue, including minimizing the risk of addiction to opioid painkillers prescribed for pain and inflating the number of Americans struggling with pain. They also influenced the creation of a new stigmatized identity: the doctor unwilling to prescribe opioids for patients in pain.

The American Pain Foundation, a medical society for doctors who treat pain, received 90 percent of its $5 million funding in 2010 from the drug and medical device industry. The extent to which other pain societies might have been subsidized by Big Pharma is unclear, but according to an article published in *ProPublica* in 2012, US senators Baucus and Grassley launched an investigation into the American Pain Foundation,

the American Academy of Pain Medicine, the American Pain Society, the Wisconsin Pain and Policy Group, and the Center for Practical Bioethics, exploring the extent to which drug manufacturers such as Purdue Pharma, Endo Pharmaceuticals, and Johnson and Johnson might have encouraged these societies to promote opioid painkiller prescribing.[90]

The American Pain Society, founded in 1995 with Dr. Portenoy as its first president, issued treatment guidelines urging doctors to prescribe more opioids for the treatment of pain. Their self-proclaimed goal was to cure the medical community of its "opioiphobia" (fear of prescribing opioids). The American Pain Society and the American Academy of Pain Medicine published a consensus statement in 1997 which proclaimed there was insufficient evidence to conclude that opioids, when prescribed for the treatment of pain, can result in opioid addiction.[91]

In 2011, the Institute of Medicine (IOM) committee, commissioned by the US Congress, issued a report called "Relieving Pain in America." In it, they declared that 100 million Americans—nearly a third of the population—suffer from chronic debilitating pain, at a cost of $600 billion a year in medical treatments and lost productivity.[92] They also claimed that a "cultural transformation" was necessary to improve pain management. However, the number 100 million was an exaggeration, the real number being closer to 25 million Americans with debilitating pain, or approximately 15 percent of the population.[93] Twenty-five million is still a high number of individuals in pain, and these patients need and deserve medical attention. But the cultural transformation the IOM report demanded had already occurred, to the point that doctors were engaging in excessive opioid prescribing.

In 2010 the International Association for the Study of Pain (IASP) issued a declaration stating that all patients are entitled to "access to pain management without discrimination . . . on the basis of age, sex, gender, medical diagnosis, race or ethnicity, religion, culture, marital, civil, or socioeconomic status, sexual orientation, and political or other opinions"; and "appropriate treatment includes access to pain medications, including opioids and other essential medications for pain."[94] This

statement reads more like a patient bill of rights than a policy guideline, illustrating how the campaign to destigmatize the use of opioid therapy turned into a campaign to stigmatize any doctor who wasn't prescribing opioids for pain. Opioids, doctors were told, needed to be prescribed for all forms of pain, at ever-increasing doses, lest the doctors risk engaging in unethical, discriminatory practices.

The Role of the Federation of State Medical Boards

The Federation of State Medical Boards (FSMB) is a national organization that oversees the seventy medical and osteopathic boards of the United States and its territories. The state board organizations serve many functions, one of which is to police doctors and exert disciplinary action against doctors who are deemed dangerous to patients. One of the most severe forms of disciplinary action is to revoke a doctor's license to practice medicine.

In 1998, the FSMB issued a policy to reassure doctors that they would not be prosecuted if they prescribed even large amounts of opioids, as long as it was for the treatment of pain. In 2001, every licensed physician in the state of California was mandated to attend a day-long course on the treatment of pain as a requirement to maintain licensure. The federation urged state medical boards to punish doctors for undertreating pain. Doctors lived in fear of disciplinary action from the board, and the lawsuit that usually followed, if they denied a patient opioid painkillers. In 1991 in North Carolina, in the case of *Henry James v. Hillhaven*, $7.5 million was granted to the family because a nurse did not follow the doctor's order to properly address pain. In 1998 in California in the case of *Bergman v. Eden Medical Center*, $1.5 million was granted to the family because the physician did not properly address the patient's pain.

The FSMB published a book promoting the use of opioid painkillers. This book was funded by Purdue Pharma, Endo Health Solutions,

and others, with proceeds totaling $280,000, and was developed with the help of David Haddox, a senior Purdue Pharma executive.[81] The federation admitted to receiving nearly $2 million dollars from opioid makers since 1997 to support its efforts.[81]

The Role of the Joint Commission on Accreditation of Healthcare Organizations

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO), often simply referred to as "The Joint Commission" (TJC), is a United States–based nonprofit tax-exempt 501(c) organization that accredits health care organizations and programs in the United States. The Joint Commission arose out of a movement in the 1950s to reform hospitals by looking at whether or not patients got better. JCAHO went through a consolidation of power over the years, combining multiple medical organizations under one roof, simplifying its name in 2007 to "The Joint Commission." Its mission statement is "Helping Health Care Organizations Help Patients."

Today, having Joint Commission accreditation is required for many hospitals and clinics to remain licensed. Payment for services from the Centers for Medicare and Medicaid Services (CMS), the largest federally funded insurance program, is also contingent on TJC approval. TJC approval is obtained through periodic surveys. Huge amounts of time and large sums of money are devoted to preparing for these surveys, which hospitals must pay TJC to perform.

These surveys assess adherence to "best practices." Best practices are defined by TJC itself: "Joint Commission standards are developed with input from health care professionals, providers, subject matter experts, consumers, government agencies (including the Centers for Medicare & Medicaid Services) and employers. They are informed by scientific literature and expert consensus and reviewed by the Board of Commissioners. New standards are added only if they relate to patient

safety or quality of care, have a positive impact on health outcomes, meet or surpass law and regulation, and can be accurately and readily measured."[95]

In 2001, The Joint Commission made "pain" the fifth vital sign, alongside heart rate, temperature, respiratory rate, and blood pressure, indicating the state of a patient's essential body functions. Pain, however, unlike the original vital signs, cannot be objectively measured. Thus, TJC promoted the use of the Visual Analog Scale of pain assessment (a series of happy and sad faces corresponding to degrees of pain), accompanied by a number on a scale from 1 to 10, with 10 out of 10 pain being the worst pain a human being could endure and 1 the pain equivalent of, let's say, a stubbed toe. Quantifying pain made it possible to standardize procedures across doctors and met TJC's own requirement of implementing new standards only if they could "be accurately and readily measured."

Despite the appearance of objectivity, the Visual Analog Scale and the numerical pain scale represent entirely arbitrary measurements. There is in fact no way to measure a person's pain. One person's severed leg might be a 1 on the pain scale, and another person's stubbed toe a 10. Furthermore, no scientific studies show that using these pain scales correlates with improved patient outcomes. Data do show, however, that use of these pain scores increases opioid prescribing and opioid use.[96, 97]

The Joint Commission launched a nationwide "pain management educational program." They sold educational materials to hospitals so they could meet the standards of pain treatment that would be required to pass the next Joint Commission Survey.[98] These materials included laminated cards and posters of the Visual Analog Scale of pain, as well as teaching videos promoting more liberal prescribing of opioids for pain: "Some clinicians have inaccurate and exaggerated concerns about addiction, tolerance and risk of death. . . . This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control."[99] Many of these teaching

materials were produced by Purdue Pharma, the makers of OxyContin, and given to TJC, free of charge.

A Government Accountability Report, published in 2003, had this to say about the relationship between TJC (herein referred to as JCAHO) and Purdue Pharma:

> From 1996, when OxyContin was introduced to the market, to July 2002, Purdue has funded over 20,000 pain-related educational programs through direct sponsorship or financial grants. These grants included support for programs to provide physicians with opportunities to earn required continuing medical education credits, such as grand round presentations at hospitals and medical education seminars at state and local medical conferences. During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff on how to comply with JCAHO's pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO's pain management educational programs. Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO's Web site. Purdue's participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin. [98]

In 2012, The Joint Commission published a report on the safe use of opioids in hospitals, publicly recognizing the need for improved patient assessment and management to lower the incidence of opioid overdose in the inpatient setting.[100]

The Role of the Food and Drug Administration

The Food and Drug Administration (FDA) is an agency within the US Department of Health and Human Services responsible for assuring the safety, effectiveness, and quality of medical drugs. They are responsible

for approving drugs before they reach the market and monitoring the safety and marketing of those drugs once they have become available to the public. The FDA contributed to the prescription opioid painkiller epidemic by failing to prevent drug companies from promoting opioid painkillers in the treatment of chronic pain, for which there was little evidence, and by making it easier for pharmaceutical companies to get FDA approval for new opioids coming on the market.

Every pharmaceutical company that seeks FDA approval for a particular drug must demonstrate to the FDA in a series of clinical trials (studies) that their drug is better than a placebo (a sugar pill) and that, whatever side effects posed by the drug, the potential benefits (for a given population of patients) outweigh the risks. In the late 1990s, the FDA implemented a new study protocol for FDA approval called "enriched enrollment," which it said would result in smaller studies, shortened drug development time, and lower development costs for the pharmaceutical industry. The investigative journalist John Fauber, writing for the *Wisconsin Sentinel*, said the decision to change study requirements arose from a series of meetings over more than a decade between experts in pain medicine, primarily from academia, and representatives of the FDA. The invitation-only meetings were sponsored by Big Pharma, which paid up to $35,000 for drug company representatives to attend, raising "serious questions about the way in which federal regulators interact with the pharmaceutical companies they regulate."[101] The enriched enrollment protocol does appear to be a way for drug companies to cheat, getting approval for opioid painkillers that don't really work.

In traditional studies that assess the benefit of a drug as compared with a placebo, participants are randomly assigned to participate in one group or the other. The random assignment of the participants is fundamental to good clinical studies because it insures that neither group is predisposed to do better, or worse, on the drug or placebo, than the other. With this traditional design, opioid medications in the treatment of chronic pain were not performing well. This was happening for

a number of reasons. First, a lot of patients on opioids were dropping out of the study due to side effects, such as dizziness, constipation, nausea, or vomiting. Second, participants in the placebo group were doing better, in part because they weren't having the side effects. Placebo, it turns out, is pretty good medication for chronic pain. Drug companies were understandably frustrated because they were not getting the results necessary for FDA approval. So the study design was revised. The new design, which persists today, is called "enriched enrollment."

With enriched enrollment, instead of giving half of the participants the study drug and half the placebo, investigators give everyone the study drug in what is called the "open-label phase," because both researchers and participants can see the metaphorical label on the pill bottle and know the subject is getting an opioid. During this open-label phase, as many as half of the participants typically drop out due to side effects and opioid intolerance, or maybe just because opioids are not a good medicine for chronic pain. The people left in the study are all the people who are on some level benefitting from the opioids. At the end of the open-label phase, all the participants are tapered down and off opioids, and re-randomized to two groups, opioid or placebo.

Enriched enrollment is a flawed design because the study population is not generalizable to all chronic pain patients but only to chronic pain patients who already like opioids. The study is also no longer double blind because the participants who continue to experience opioid withdrawal, which can go on for weeks and months in some people, continue to feel worse when they're randomized to placebo. What naturally ends up happening is that many of the individuals who liked being on opioids and who are randomized to placebo end up dropping out of the study, so now the dropout rate is higher in the placebo arm than in the study-drug arm. The result is that the opioid study drug ends up looking better than placebo, and the drug gets approved by the FDA.

Here's an analogy. Imagine you are testing a theory that, to keep kids happy and well-behaved during lunchtime recess, playing soccer is better than engaging in arts and crafts. You take the entire third-grade

class and randomly, by drawing names from a hat, divide the students into two groups: half to play soccer and half to sit at the arts and crafts table and make hand puppets. At the end, you use some measure to assess whether kids are happier and better behaved when they play soccer or when they do art. That is a classic randomized study design.

Now suppose that instead of the above, you make all the kids play soccer every day at lunch for two weeks first, before randomizing them to different groups. Naturally, the kids who already like soccer or are more athletic or have higher energy will probably enjoy this. The kids who are naturally unathletic, low-energy, or disinclined to play sports will not like this. In fact, quite a few of them may simply refuse to participate and may even bring in notes from their parents asking that they be allowed to sit out during lunch. At the end of the two weeks, you might have only half the number of kids still playing soccer because the rest have dropped out of the study. All clinical studies have subjects who drop out, ending with many fewer subjects than when the study started.

With the kids left, most of whom enjoy soccer, you now randomly assign half to soccer, and half to arts and crafts. The kids who get randomized to soccer are happy. The ones who get randomized to arts and crafts are not so happy. They miss soccer and are now also fidgety and restless because their bodies had gotten used to getting exercise during lunch. Your study results unequivocally show that kids who play soccer are much happier and better behaved than kids who do arts and crafts, and every school in the district, as a result of your work, has mandatory soccer at lunchtime.

The FDA has made some limited innovations to target the prescription opioid epidemic, but for every step forward, they've taken two back. In 2014, the FDA reclassified Vicodin, among the most misused painkillers in the 1990s and early 2000s, to schedule II, making it harder for doctors to prescribe it and hence for patients to get it.[102] But nearly simultaneously, in 2013, the FDA approved Zohydro, a long-acting version of Vicodin that is likely to be as addictive as or more addictive than

Vicodin. The FDA is meanwhile keeping drugs like Opana on the market. Opana was approved in 2011 as an "abuse-deterrent" opioid painkiller, but since then has proven to be highly addictive when injected. It was recently tied to a 2015 outbreak of HIV in rural Indiana, as well as a surge in hepatitis C infections in Kentucky, Tennessee, West Virginia, and Virginia.

The Engine and the Caboose

In 2007 three of Purdue's top executives pleaded guilty to "misbranding" OxyContin as less addictive than it is, and Purdue paid $634 million in fines, the eleventh largest fine paid by a pharmaceutical firm in the history of the US Department of Justice. Of the fines paid by Purdue in 2007, about $160 million went to reimburse the federal government and some states for damages suffered by Medicaid programs, the government health insurer for the poor.[103]

Kentucky, one of the states especially hard hit by the prescription opioid epidemic, refused its reimbursement of $500,000, the only state to do so, deciding instead to file its own class action lawsuit against Purdue. Similar class action suits have been filed by Illinois and California. When Kentucky's suit against Purdue goes to trial, it will be an unprecedented event. Purdue Pharma has never gone to trial for OxyContin and has succeeded in dismissing more than four hundred personal injury lawsuits related to the use of OxyContin. If Kentucky wins, Purdue is facing an extraordinary fine, comparable to the class action suits that cost Big Tobacco billions in the 1990s. Unfortunately, it's too little too late for the 175,000 people who have died from prescription opioid overdose between 1999 and 2013, not to mention the lives lost before and after.

Manufacturers of opioid painkillers have contributed to the opioid epidemic that has ravaged the United States, but blame cannot be placed on Big Pharma alone. Blame lies with doctors as well, especially those in academia and other positions of leadership who ignored the

evidence on risk and efficacy in pursuit of their own agenda—an agenda that originated in a desire to help but then lost its way. Blame also lies with regulatory agencies like the Federation of State Medical Boards, The Joint Commission, and the FDA, which blindly followed the lead of the pharmaceutical industry, propagated misinformation, and failed to do their jobs: to regulate.

Big Medicine was the engine behind the opioid paradigm shift, and Big Pharma the stealthy and powerful caboose. Big Medicine provided legitimacy, and Big Pharma the funds to push the message along. Neither anticipated the success of their partnership, nor the runaway train it would become when the opioid epidemic took over.